MINIATURIZED SAMPLE PREPARATION TECHNIQUES USING MCM-41-BASED MATERIALS IN THE ANALYSIS OF SELECTED NON-STEROIDAL ANTI-INFLAMMATORY AND ANTI-DEPRESSANT DRUGS

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In the name of Allah, the Most Merciful and the Most Beneficent.

This thesis is dedicated to my beloved parents and husband,

Kamaruzaman bin Abdullah, Siti Mahani Muhammad and

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ABSTRACT

New approaches in miniaturized sample preparation have been investigated involving the use of mesoporous silica materials as adsorbents. Mesoporous silica MCM-41 was successfully synthesized from rice husk ash as an active source of silica and a few mg of the material was enclosed within a cone-shaped membrane for solid phase membrane tip extraction (SPMTE). Four non-steroidal anti-inflammatory drugs (NSAIDs) namely ketoprofen, mefenamic acid, naproxen and diclofenac were selected as target analytes. Under the optimized conditions the proposed MCM-41-SPMTE method provides good limits of detection (LODs) for analytes in human urine samples in the range of 5.7 - 10.6 µg/L and relative analyte recoveries in the range of 81.4 - 108.1% that are comparable with those of conventional solid phase extraction (SPE) method. A simple microextraction technique utilizing a mixed matrix membrane (MMM) as the extraction medium has been successfully demonstrated. Thiol-functionalized MCM-41 adsorbent was immobilized in the cellulose triacetate polymer matrix through dispersion method to form a thiol-MCM-41-MMM. Three NSAIDs namely diclofenac, mefenamic acid and ibuprofen were used as target analytes. The results showed good relative recoveries (85.9 - 106.7%) with relative standard deviation (RSDs) < 8% (n = 9), and low LODs (0.04 - 0.19 µg/L) for spiked river and tap water samples. The newly developed method is a simple, feasible, and cost effective and showed results that are comparable with conventional SPE. The use of MCM-41 magnetized with iron oxide particles (Fe_3O_4) in magnetic solid phase extraction (MSPE) method has been investigated. The developed Fe_3O_4-MCM-41-MSPE method was applied to the extraction of two anti-depressant drugs (amitriptyline and chlorpromazine) in human urine and plasma samples prior to gas chromatography–mass spectrometry (GC–MS) analysis. Under the optimized conditions, the results provided good relative recoveries (86.1 - 115.4%), good reproducibility with relative standard deviation (RSDs) < 10% (n = 5) and low LODs for both spiked urine (0.015 - 0.017 µg/L) and plasma (0.020 - 0.028 µg/L) samples. This method proved to be rapid and efficient, for the multi-analysis of the drugs in biological samples. A novel procedure involving sonication-assisted emulsification microextraction (SAEM) followed by Fe_3O_4-MCM-41-MSPE prior to HPLC-UV has been developed for the analysis of anti-depressant drugs (amitriptyline, chlorpromazine and imipramine) from biological and water samples. In the SAEM procedure, 1-octanol and 3 min were selected as emulsification solvent and extraction time, respectively. Under the most favorable conditions, the method showed good limits of detection (as low as 0.04 µg/L) and reproducibility of extraction (RSDs < 10.6%, n = 3). The proposed methods provide alternative approaches in sample preparation through different microextraction methods to solve analytical problems that are not easily addressed by the individual procedure alone.

ABSTRAK

Pendekatan baharu dalam penyediaan sampel mini telah dikaji dengan melibatkan penggunaan bahan silika mesoliang sebagai penjerap. Silika mesoliang MCM-41 telah berjaya disintesis daripada abu sekam padi sebagai sumber silika aktif dan beberapa mg bahan ini telah diisi ke dalam membran berbentuk kon untuk pengekstrakan muncung membran fasa pepejal (SPMTE). Empat ubat anti-radang bukan steroid (NSAIDs) iaitu ketoprofen, asid mefenamik, naproxen dan diklofenak telah dipilih sebagai analit sasaran. Di bawah keadaan optimum, kaedah MCM-41-SPMTE yang dicadangkan telah menghasilkan had pengesanan yang baik bagi analit dalam sampel urin manusia dalam julat 5.7 - 10.6 μg/L dan relatif perolehan semula analit di dalam julat 81.4 - 108.1% yang setanding dengan kaedah konvensional pengekstrakan fasa pepejal (SPE). Satu teknik pengekstrakan mikro ringkas menggunakan membran campuran matrik (MMM) sebagai medium pengekstrakan telah berjaya dibuktikan. Bahan penjerap MCM-41 terfungsitiol telah dipegunkan ke dalam matriks polimer triasetat selulosa melalui kaedahserakan untuk membentuk tiol-MCM-41-MMM. Tiga NSAIDs iaitu diklofenak, asid mefenamik dan ibuprofen telah dipilih sebagai analit sasaran. Keputusan menunjukkan perolehan semula relatif (85.9 - 106.7%) dan sisihan piawai relatif, RSDs yang baik < 8% (n = 9) dan had pengesanan yang rendah (LODs) (0.04 - 0.19 μg/L) bagi sampel air sungai dan air paip pakuan. Kaedah baharu yang dibangunkan ini adalah ringkas, boleh dilaksanakan dan menjimatkan kos dan menunjukkan keputusan yang setanding dengan kaedah SPE konvensional. Penggunaan MCM-41 termagnet dengan zarah ferum oksida (Fe_3O_4) dalam kaedah pengekstrakan fasa pepejal bermagnet (MSPE) telah dikaji. Kaedah Fe_3O_4-MCM-41-MSPE yang dibangunkan ini telah digunakan untuk pengekstrakan dua ubat anti-murung (amitriptilina dan klorpromazin) dalam sampel urin dan plasma manusia sebelum analisis kromatografi gas-spektrometri jisim (GC-MS). Di bawah keadaan optimum, keputusan menunjukkan perolehan semula relatif yang baik (86.1 - 115.4%), kebolehulangan semula yang baik dengan sisihan piawai relatif RSDs < 10%, (n = 5) dan had pengesanan yang rendah bagi kedua-dua sampel urin (0.015 - 0.017 μg/L) dan plasma (0.020 - 0.028 μg/L) pakuan. Kaedah ini terbukti cepat dan cekap untuk analisis berbilang ubat di dalam sampel biologi. Satu prosedur novel melibatkan pengekstrakan mikro pengemulsian bantuan sonik (SAEM) diikuti dengan Fe_3O_4-MCM-41-MSPE sebelum HPLC-UV telah dibangunkan untuk menganalisis ubat anti-murung (amitriptilina, klorpromazin dan imipramina) daripada sampel biologi dan air. Dalam prosedur SAEM, 1-oktanol dan 3 minit telah dipilih sebagai pelarut pengemulsian dan masa pengekstrakan. Di bawah keadaan paling sesuai, kaedah ini menunjukkan had pengesanan (serendah 0.04 μg/L) dan kebolehulangan semula yang baik (RSDs < 10.6%, n = 3). Kaedah yang dicadangkan ini menyediakan pendekatan alternatif dalam penyediaan sampel melalui kaedah pengekstrakan mikro yang berbeza untuk menyelesaikan masalah analisis yang tidak mudah diatasi oleh prosedur individu sahaja.

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LIST OF ABBREVIATIONS

ACN	-	Acetonitrile
BET	-	Brunauer-emmett-teller
CAR	-	Carboxen
CE	-	Capillary electrophoresis
CHF	-	Continuous hollow fiber
CNTs	-	Carbon nanotubes
CTA	-	Cellulose triacetate
CTABr	-	Hexadecyltrimethylammonium bromide
CW	-	Carbowax
DAD	-	Diode array detector
DIC	-	Diclofenac sodium
DI-SPME	-	Direct immersion solid phase microextraction
DLLME	-	Dispersive liquid-liquid microextraction
DSPE	-	Dispersive solid phase extraction
DVB	-	Divinylbenzene
EF	-	Enrichment factor
EME	-	Electromembrane extraction
ER	-	Enrichment recovery
EtOH	-	Ethanol
Fe_3O_4	-	Iron (III) Oxide / Magnetite
FESEM	-	Field emission scanning electron microscope
FID	-	Flame ionization detector
FTIR	-	Fourier transform infrared
GC	-	Gas chromatography
HCl	-	Hydrochloric acid
HF	-	Hollow fiber
HPLC	-	High performance liquid chromatography

HS	-	Headspace
IBU	-	Ibuprofen
IL	-	Ionic liquid
IPA	-	Isopropyl alcohol
KET	-	Ketoprofen
LC	-	Liquid chromatography
LD	-	Liquid desorption
LLE	-	Liquid-liquid extraction
LLLME	-	Liquid-liquid-liquid microextraction
LOD	-	Limit of detection
LOQ	-	Limit of quantification
LPME	-	Liquid phase microextraction
MAE	-	Microwave assisted extraction
MAOIs	-	Monoamine oxidase inhibitors
MCM	-	Mobil crystalline materials
MEF	-	Mefenamic acid
MeOH	-	Methanol
MEPS	-	Microextraction in packed syringe
MIP	-	Molecularly imprinted polymer
MMMs	-	Mixed matrix membrane
MPs	-	Magnetic particles
MPTMS	-	3-mercaptopropyltrimethoxysilane
MS	-	Mass spectrometry
MS/MS	-	Tandem mass spectrometry-mass spectrometry
MSPD	-	Matrix solid phase dispersion
MSPE	-	Magnetic solid phase extraction
MWCNTs	-	Multiwall carbon nanotubes
NaCl	-	Sodium chloride
NaOH	-	Sodium hydroxide
NAP	-	Naproxen
NMR	-	Nuclear magnetic resonance
NSAIDs	-	Non-steroidal anti-inflammatory drugs
PA	-	Polyacrylate

PAHs	-	Polycyclic aromatic hydrocarbons
PDMS	-	Polydimethylsiloxane
PP	-	Polypropylene
PTFE	-	Polytetrafluoroethylene
RAM	-	Restricted access materials
RHA	-	Rice husk ash
RP-HPLC	-	Reversed phase-high performance liquid chromatography
RR	-	Relative recovery
RSD	-	Relative standard deviation
SAEM	-	Sonication assisted emulsification microextraction
SBA-15	-	Santa Barbara Amorphous No 15
SBSE	-	Stir bar sorptive extraction
SDME	-	Single drop microextraction
SFO	-	Solidification of floating organic
SIM	-	Selected ion monitoring
SPE	-	Solid phase extraction
SPME	-	Solid phase microextraction
SPMTE	-	Solid phase membrane tip extraction
SSRIs	-	Selective serotonin reuptake inhibitors
TCAs	-	Tricyclic anti depressant drugs
TD	-	Thermal desorption
TEOS	-	Tetraethylorthosilicate
TF-SPME	-	Thin film-solid phase microextraction
THF	-	Tetrahydrofuran
UPLC	-	Ultra performance liquid chromatography
UV	-	Ultraviolet
VA-μ-SPE	-	Vortex assisted-micro-solid phase extraction
XRD	-	X-ray diffraction
μ-SPE	-	Micro-solid phase extraction

LIST OF SYMBOLS

A	-	Analyte
g	-	Gram
g/mol	-	Gram per mol
h	-	Hour
I.D.	-	Internal diameter
K	-	Partition coefficient
L	-	Liter
m	-	Meter
mg	-	Milligram
min	-	Minutes
mL	-	Milliliter
mL/min	-	Milliliter per minute
mm	-	Millimeter
mmol	-	Millimole
n	-	Amount of analyte extracted by the coating
ng	-	Nanogram
nm	-	Nanometer
pKa	-	Acid dissociation constant
ppb	-	Part per billion
R	-	Correlation coefficient
rpm	-	Rotation per minute
s	-	Second
v/v	-	Volume per volume
V_o	-	Volume of organic extraction solvent
V_s	-	Sample volume
V_w	-	Volume of aqueous sample solution
w/v	-	Weight per volume

%	-	Percent
°C	-	Degree celcius
µg	-	Microgram
µL	-	Microliter
µg/L	-	Microgram per liter
µg/mL	-	Microgram per liter
µm	-	Micrometer

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Drugs have played a very important role in the process of human civilization for treating and preventing diseases. Today, most of the drugs used are synthetic origin and they are widely used for their therapeutic effects in pharmaceutical formulations. There are biologically active chemical substances generally formulated into convenient dosage forms such as tablets, capsules, suspensions, ointments and injectable (Rao and Nagaraju, 2003). Up to now, there is no single, precise definition, as there are different meanings in drug control law, government, regulations, medicine, and colloquial usage. In environment, the health effect that may cause the living organism is not easy to predict due to lack of ecotoxicological data available and less critical research have been done on the risk assessment.

Biological and environmental sample matrices are complex and often contain interfering elements and organic compounds that can mask or interfere with the compounds of interest, thus, direct analysis may not be possible. Moreover, the drugs often exist at low concentration in biological and environmental samples. Thus, it is necessary to perform a preliminary step of concentration and purification of the analytes prior to their analysis.

Nowadays, there are many sample preparation techniques that have been developed and all of them share the same fulfilments which are to remove potential interfering elements, to enrich the concentration of the target compound or analyte,

to convert an analyte into a more suitable form (if necessary), to reduce or eliminate the volume of organic solvents and to provide a robust, reproducible method that is suitable for all of the sample matrices (Smith, 2003).

Traditional sample preparation techniques such as liquid–liquid extraction (LLE) and solid phase extraction (SPE) have been widely used in analytical field. However, these methods have their own disadvantages, such as the requirement for large amounts of sample and organic solvent, involving the multi-step procedures which led to the time-consuming and as well as utilizing most of the harmful chemicals which are costly to dispose.

Recently, considerable interest has been focused on the miniaturization and utilizing solventless sorptive samples preparation methods for the drugs analysis. Basically, the sample preparation techniques can be categorized into two parts according to the different extraction phases used which are solvent-based microextraction and material/sorbent-based microextraction.

Liquid-phase microextraction (LPME) is a solvent-based extraction first introduced by Jeannot and Cantwell (1996). LPME is based on the equilibrium extraction procedure and only a small fraction of the analytes was extracted for the analysis. LPME technique has been established either by extraction into small water immiscible drops of organic solvents (microdrop) or into small volumes of acceptor solution present inside the lumen of porous hollow fibers (Rasmussen and Pedersen-Bjergaard, 2004). LPME proved to be a solventless, simple and cost-effective microextraction setup which obtains a high enrichment of analytes, high selectivity and eliminating the possibility of carry over between the run.

Apparently, the introduction and development of new materials/sorbents for microextraction have promising alternative to overcome some problems occurred in analytical chemistry field. This microextraction is called sorbent/material-based microextraction. Solid-phase microextraction (SPME) is one of the solventless microextraction techniques that dramatically simplifies the sample preparation

procedures by combining the integration of sampling, isolation and enrichment in one step (Pawliszyn, 1997). However, despite these advantages, SPME has some disadvantages, it suffers from long extraction and desorption time to reach equilibrium, fragility and limited lifetime of fibre and the possibility of sample carry-over (Lambropoulou and Albanis, 2007).

Stir bar sorptive extraction (SBSE) was developed by Sandra's group as a powerful alternative sample preparation technique in 1999 (Baltussen *et al.*, 1999). In SBSE procedure, a stir-bar coated with a thick-layer of polydimethylsiloxane (PDMS) is inserted into the sample solution for performing the extraction. The extraction principle of SBSE is similar to the SPME. SBSE proved to be more sensitive compared to the SPME. These might be due to a larger amount of PDMS relative to the SPME fibre which increases the recovery of analyte extracted into the extractant phase. However, it should be noted that, the conventional commercially available stir bar-coated with PDMS is only effective towards extracting the nonpolar compounds.

Currently, SPE, SPME and SBSE methods are the most popular sorbent-based extraction techniques used. Unfortunately, commercially available sorbent materials are limited and effective only towards any particular class of analytes; thus, various types of sorbents which are universally applicable should be explored.

Recently, the applications of mesoporous silica materials in sample preparation have gained a lot of attention from researchers (Wang *et al*., 2013). These might be due to the larger pore volumes and higher surface areas which provide the sufficient capacity for the adsorption of analytes. In addition, mesoporous silica materials possess thermal stability, chemical stability, compositional controllability, as well as the flexibility in post synthesis modifications to enable the further introduction of hydrophilic, hydrophobic, polar as well as positive or negatively-charged functional moieties on the surface of the materials (Zhao *et al*., 2012).

1.2 Problem Statement

In the last two decades, efficient and sensitive analytical instrumentation have been introduced for various applications. However, sample preparation today remains considered as the most crucial step in the whole analytical process. Numerous sample preparation techniques have been developed with the following main goals: to improve the selectivity in extraction, to minimize the initial sample sizes, to facilitate the automation and to reduce or eliminate the volume of organic solvent involved in the extraction (Curylo *et al*., 2007; Smith, 2003).

Based on the aims of sample preparation techniques, traditional LLE method does not fulfill current requirements and it has been displaced by new extraction techniques such as SPE, SPME, SBSE, LPME and more recently by micro solid-phase extraction (μ-SPE), magnetic solid phase extraction (MSPE), dispersive solid phase extraction (DSPE), solid phase membrane tip extraction (SPMTE) or dispersive liquid-liquid microextraction (DLLME). Several comprehensive reviews on the current advances in sample preparation field and emphasizing the importance of sample preparation in the analytical process have been published (Turiel and Martín-Esteban, 2010; Augusto *et al*., 2010).

The various established extraction methods have their own advantages and drawbacks. Currently, SPE and SPME are widely used in analytical field. Nevertheless, the lack of selectivity of the commercial available sorbents in SPE and SPME has rendered their applications become economically unattractive. In addition, for SPE, a critical optimization should be carried out for each step (conditioning, sample loading, washing and elution) and that leads to a time-consuming process. For SPME, unfortunately, long extraction and desorption time is required for a complete analysis.

In recent years, mesoporous silica materials with high surface area and pore volume have been employed as alternative sorbents in sample preparation. The usefulness of these materials is manifested in their mesostructures which allows bulky organic molecules access to the larger internal surface and cavities that

enhance adsorptive capacity and selectivity. In this study, MCM-41 and functionalized-MCM-41 were synthesized and characterized. An agriculture waste, rice husk ash (RHA) was utilized as the silica source to produce MCM-41. Comprehensive studies on the applicability of the synthesized mesoporous silica materials as adsorbents in various microextraction techniques were conducted. The applicability of the developed methods was examined in the determination of selected acidic and basic drugs in biological and environmental water samples.

1.3 Research Objectives

The aim of this study is to develop miniaturized sample preparation techniques utilizing mesoporous silica materials as adsorbents for the analysis of drugs in different types of matrices. The objectives of this research are as follows:

(a) To develop MCM-41 solid phase membrane tip extraction (MCM-41-SPMTE) coupled with liquid chromatography for the analysis of selected non-steroidal anti-inflammatory drugs (NSAIDs) in human urine samples.

(b) To develop micro-solid phase extraction (μ-SPE) based on thiol-MCM-41 mixed matrix membranes (MMMs) for the analysis of NSAIDs in river and tap water samples.

(c) To develop a magnetic solid phase extraction (MSPE) utilizing magnetite MCM-41 (Fe_3O_4-MCM-41) coupled with gas chromatography for the determination of selected anti depressant drugs in biological and water samples.

(d) To develop a combined sonication-assisted emulsification microextraction (SAEM) and Fe_3O_4-MCM-41 magnetic solid phase extraction (MSPE) coupled with high performance liquid chromatography for the analysis of selected anti depressant drugs in biological and water samples.

1.4 Scope of the Research

Preparation, characterization and application of MCM-41, thiol-MCM-41, thiol-MCM-41-MMM and magnetite-MCM-41 in various microextraction techniques were studied. The synthesized materials were characterized using Fourier transform infrared (FTIR), X-ray diffraction (XRD), Field emission scanning electron microscopy (FESEM) and nitrogen adsorption-desorption analysis. Several NSAIDs and anti-depressant drugs were selected as model analytes. Several extraction parameters were comprehensively optimized and the optimum conditions were applied to the analysis of analytes in biological (human urine and plasma) and environmental (river water, tap water and lake water) samples.

1.5 Significance of Research

Unlike priority pollutants, the behavior of drugs in the environmental and biological samples has not been studied extensively. Many microextraction techniques have been proposed and utilized for the analysis of drugs in biological and environmental samples. Most of the well-established sample preparation methods in analytical processes have the same goals since the last century which are to improve the speed and reduce the cost of the methods, eliminate or reduce the organic solvent usages and if possible to provide better sensitivity and selectivity for the quantitation of drugs.

In this study, mesoporous silica materials namely MCM-41 and functionalized-MCM-41 were synthesized from an agricultural waste. This research will contribute suitable method for the separation, extraction, and detection of selected drugs in complex samples. Through this work, various alternative microextraction methods for the analysis of drugs can be carried out effectively with environmental benignity because they use small amounts of organic solvents and the preparation of adsorbent and microextraction setup are simple and cost effective. Besides, this research will be useful for the establishment of more rapid and efficient methods for the detection of drugs during treatments and forensic analysis.

1.6 Outline of the Thesis

This thesis consists of seven chapters. Chapter 1 describes in details the research background, problem statement, objectives, scope as well as significance of the study. Chapter 2 compiles the literature review, the details regarding the conventional extraction and microextraction techniques, introduction to the mesoporous silica materials and last but not least the classification of selected drugs studied.

Chapter 3 describes the experimental methodology of synthesis, characterization and application of MCM-41 in SPMTE for the analysis of four selected NSAIDs namely ketoprofen, mefenamic acid, diclofenac and naproxen in human urine. Several important extraction parameters such as types of organic conditioning solvent, sample pH, salting-out effect, extraction time, sample volume, desorption solvent and desorption time were optimized. The separation of the NSAIDs was studied by HPLC-UV using C_{18} column.

Chapter 4 elaborates the experimental methodology of the preparation, characterization and application of thiol-MCM-41-MMM as adsorbent in μ-SPE for the determination of three selected NSAIDs (diclofenac, mefenamic and ibuprofen) in environmental samples. Several important extraction parameters such as sample pH, salting-out effect, extraction time, sample volume, desorption solvent and desorption time were optimized.

Chapter 5 reports the experimental methodology of synthesis, characterization and application of Fe_3O_4-MCM-41-MSPE coupled with GC-MS for the analysis of anti-depressant drugs in urine and plasma samples. Several important parameters that might affect the extraction efficiency of the developed method were investigated including extraction time, vortex speed, desorption solvent, desorption time, sample pH and effect of salt addition.

Chapter 6 describes the experimental methodology of the application of sonication-assisted emulsification microextraction (SAEM) and Fe_3O_4-MCM-41-MSPE for the determination of three selected anti-depressant drugs (amitryptiline, chlorpromazine and imipramine) in urine, lake and tap water samples by HPLC with ultraviolet detection. Finally, Chapter 7 summarizes the overall results obtained with suggestions for future work.

first time that MCM-41 is incorporated with cellulose triacetate (CTA) to form a membrane, further investigations could be carried out by synthesizing MCM-41 with another organic functional group depending on the analytes of interest and incorporated with CTA to form a membrane. Apart from that, in this study, the membrane tumbled freely in the sample solution during the extraction. A new approach of combining thiol-MCM-41-MMM with other additives and converting into filter type membrane for the extraction and preconcentration of analytes could be another interesting alternative for this extraction.

In the last two parts, magnetite-MCM-41 has been successfully synthesized and applied in MSPE as adsorbents. The combination of two microextraction methods (SAEM-MSPE) has also been developed to achieve low detection limits of antidepressants drugs in urine and water samples. The overall enrichment efficiency can be significantly increased by increasing the sample volume or decreasing the amount of desorption solvent volume prior to the analysis. MSPE is a rapid and simple microextraction as the separation can be done by utilizing an external magnetic field. Thus, the *in-situ* extraction for the analysis of such as real-world environmental (waste or slurry) water samples would be of interest.

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